Dissertation on

Comparison of Sildenafil with Papaverine in penile Doppler by assessing hemodynamic changes

Submitted in Partial Fulfillment of Requirements for

M.D. DEGREE BRANCH VIII

RADIO DIAGNOSIS Of

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,

CHENNAI

MARCH- 2009

MADRAS MEDICAL COLLEGE AND RESEARCH INSTITUTE

CHENNAI- 600 003.

CERTIFICATE

This is to certify that DR. C.Kabilan has been a post graduate student during the period May 2006 to March 2009 at Department of Radiodiagnosis, Madras Medical College and Research Institute, Government General Hospital, Chennai.

This Dissertation titled "Comparison of sildenafil with papaverine in penile doppler by assessing hemodynamic changes" is a bonafide work done by him during the study period and is being submitted to Tamilnadu Dr.M.G.R. Medical University in Partial fulfillment of the M.D. Branch VIII RadioDiagnosis Examination

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ACKNOWLEDGEMENT

I would like to thank **Prof. T.P.Kalanithi, M.B., M.D**, Dean , Madras Medical college and Research Institute for giving me permission to conduct the study in this Institution

I would like to express my sincere and heartfelt gratitude to my Teacher and guide **Prof. N.Kulasekaran M.B., M.D, D.M.R.D** , Director,Barnard Institute of Radiology,M.M.C for having encouraged me to take up this study. But for his guiding spirit, perseverance and wisdom this study would not have been possible.

I am greatly indebted to my assistant professors

Dr. P.Umapathy D.M.R.D, D.M.R.T,

Dr.S.Sundareswaran D.M.R.D,

Dr.Nesam Manivannan D.M.R.D,

Dr.S.Kalpana M.D

Dr.S.Babu peter M.D

Dr.D.Ramesh M.D

Dr.C.Amarnath M.D

For their valuable suggestions and support

I wish to thank my fellow postgraduates for their untiring help and encouragement

I thank all my patients for their co operation, without whom this study would not have been possible.

Contents

S.NO	Title	PAGE NUMBER
1.	Introduction	1
2.	Aims and objectives	3
3.	Review of literature	4
4.	Physiology of Erection	6
5.	Performing a penile Color Doppler Ultrasonography	9
6.	Sonographic anatomy of penis	18
7.	Clinical and Doppler evaluation of erectile dysfunction	24
8.	Materials and method	44
9.	Observation	46
10.	Discussion	50
11.	Conclusion	53
12.	Bibliography	
	Annexure	
	Proforma	
	Master chart	

Introduction

Erectile dysfunction is a common complaint after the age of 40. It is rampant in this era of early onset hypertension and diabetes where in even people younger than 30 years commonly encounter the problem. The problem often goes under noticed because of the emotional aspect it has and the social stigma that has been attached with it. This fact is supported by the truth that the exact incidence of erectile dysfunction in developing countries like India is still unknown. Even then the number of cases presenting to the out patient department is going on increasing insisting the magnitude of the problem as well as the people's awareness.

Since erection involves a complex physiology, it goes with out saying that the causative factors involved in the erectile dysfunction are diverse. One traditional way of classification is in to three types, namely psychogenic, organic and mixed. Organic causes include neurogenic, hormonal, arterial, cavernosal and drug-induced. Identifying exact etiology becomes very essential because certain conditions could be treated and reversible if not completely.

Penile Doppler plays a pivotal role in the investigation process of a patient with erectile dysfunction. It is often the commonly employed modality after clinical examination and basic blood chemistry is obtained. It rules out arterial and venous causes of erectile dysfunction and local cavernosal pathologies. Routine method is to produce a pharmaco erection and studying the cavernosal arteries' Doppler wave form. Conventionally Papaverine is used as an intra cavernosal injection to induce erection.

Though till date Papaverine is the most potent erectogenic drug available in the market, it is invasive and produces side effects. Intra cavernosal injection is associated with anxiety which can dangerously affect the patient's erectile performance.

In the quest of an alternative to Papaverine we have tried Tab.Sildenafil in performing penile Doppler as an erectogenic drug.

Aims and objectives:

- To prospectively evaluate the efficacy of Tab.Sildenafil in doing penile Doppler
- To compare Tab.Sildenafil with Inj.Papaverine in penile Doppler study in terms of clinical and hemodynamic parameters

Review of literature:

There are about three clinical studies which has compared Sildenafil and Papaverine in doing penile Doppler.

Study by Aslant et al[1] at Firat university school of medicine, Turkey was the first one to compare the efficiency of oral phosphodiesterase inhibitors with intra cavernosal injection of vaso active agents. The drawback of the study was lack of concomitant Doppler and clinical assessment of erectile function.

Speel TG et al[2] did works to assess whether a single intracavernous injection (ICI) of a low dose of the combination of papaverine-phentolamine is replaceable by a high dose of the oral erectogenic agent sildenafil as mode of stimulation during pharmaco-penile duplex ultrasonography. He concluded that as mode of stimulation in penile duplex sonography, high dose sildenafil yields significantly less false positive diagnoses of 'veno-occlusive dysfunction' than intracavernous injection of the combination papaverine/phentolamine. No difference was found in the quality of the arterial response

Copel et al[3] tested the efficacy of Sildenafil with and without audio visual stimulation comparing to Inj.Papaverine. The study concluded that there was a significant increase in blood in the penile vasculature after ingestion of Sildenafil with audiovisual stimulation. But the response is clinically and hemodynamically inferior to

that with intra cavernosal vaso active agents. The study design contained a small number of sample size (thirteen subjects) and was liable to bias.

Our present study is unique in that it includes a large number of sample sizes which necessarily rules out the possibility of statistical bias. It is also very special in that it incorporates both clinical and Doppler hemodynamic response after each drug trial. Thus we were able to get a comprehensive assessment of a patient with erectile dysfunction.

Physiology of Erection

Penile erection is primarily a neurovascular event modulated by psychological and hormonal status. Sexual stimulation causes a release of neurotransmitters from the cavernous nerve terminals and relaxing factors from the endothelial cells in the penis, resulting in relaxation of smooth muscle in the arteries and arterioles supplying the erectile tissue.

Vascular Events:

A several-fold increase in blood flow occurs with a concomitant increase in compliance of the sinusoids from relaxed cavernous smooth muscle, facilitating rapid filling and expansion of the sinusoidal system against the tunica albuginea. The subtunical venular plexuses are thus compressed between the trabeculae and the tunica albuginea, resulting in almost complete occlusion of venous outflow (Fournier et al. 1987[4]; Banya[5] et al. 1989). Blood is trapped within the corpora cavernosa, which raises the flaccid penis to an erect state. Intracavernous pressures are increased to approximately 100 mmHg (the full erection phase). During sexual activity, the bulbocavernosus reflex is triggered, thus causing the ischiocavernosus muscles to forcefully compress the base of the blood filled corpora cavernosa and the penis. The penis becomes very rigid, with an intra cavernous pressure reaching several hundred mmHg (the rigid erection phase). During this phase, inflow and outflow temporarily cease. Detumescence can be the result of three separate activities: sympathetic discharge

during ejaculation, breakdown of second messengers by phosphodiesterases, or cessation of erectile neurotransmitter release. The venous channels open with contraction of the trabecular smooth muscle, therefore expelling the trapped blood and restoring flaccidity.

Nervous Events:

The penis is innervated by autonomic and somatic nerves. The somatic component is controlled by the pudendal nerve, which is responsible for penile sensation and the contraction and relaxation of the bulbocavernosus and ischiocavernosus striated muscles. Blood flow during erection and detumescence is regulated via the cavernous nerves, consisting of sympathetic and parasympathetic nerve fibers, which merge to form these nerves in the pelvis. The principal neurotransmitter for penile erection is nitric oxide, which is released from non adrenergic-noncholinergic neurotransmission of the cavernous nerves and the endothelium (Lue 2000[6]). Nitric oxide activates soluble guanylyl cyclase raising intracellular concentrations of cyclic guanosine monophosphate (cGMP). cGMP in turn activates a cGMP-specifi c protein kinase, which phosphorylates certain proteins and ion channels, resulting in opening of the potassium channels and hyperpolarization, sequestration of intracellular calcium by the endoplasmic reticulum, and inhibition of calcium channels, blocking calcium influx. The consequence is a drop in cytosolic calcium and smooth muscle relaxation/erection. During the return to the flaccid state, cGMP is hydrolyzed to guanosine monophosphate by phosphodiesterase type 5. Other phosphodiesterases are also found in the corpus cavernosum, but they do

not appear to play an important role in detumescence.

Performing a penile Color Doppler Ultrasonography

Ultrasonography:

Ultrasound evaluation of patients with erectile dysfunction should be performed in the appropriate environment, respecting the privacy of the patient. Good quality equipment and transducers suited to evaluation of superficial structures must be used.

Environment:

The sonographic examination of the patient with erectile dysfunction cannot be considered corresponding to a conventional ultrasound scanning, but requires some basic rules of privacy, avoiding all the negative factors depending on the environment, which can interfere dangerously with the erectile phenomenon (Broderick 1998[7]). An independent and dedicated ultrasound laboratory supplied with the technical requirements that can amplify or improve the action of the drugs used to induce the erection is desirable, even if not mandatory. In any case the laboratory where the examination is performed must be locked, and nobody should be allowed to enter during the examination time. Low lighting is preferable and the presence of a maximum of two medical staff. Avoiding the presence of nurses is recommended with the exclusion of the preliminary phases to reduce the negative influence of psychological factors. After the intracavernosal drug injection, the patients can be left alone before the Doppler measurements on both cavernosal arteries are performed. Once the evaluated parameters become stable, but the erection obtained is insufficient or absent, the patient is usually

left alone for some minutes and invited to stimulate the penis manually. If the degree of the rigidity obtained is less than the best spontaneous erection referred by the patient during normal sexual activity, a second dose of prostaglandin can be injected. When a venous erectile dysfunction is suspected, it is useful to ask the patient to stand and invite him to walk, because this will increase the erection and reduce the examination time. The increased erection obtained is psychologically important for the patient. To improve the drug response, audiovisual sexual stimulation has been proposed to promote smooth muscle relaxation during penile color Doppler examination. Audiovisual stimulation is performed with commercially available virtual glasses with tridimensional capabilities and stereophonic headphones. The device allows the patient to be cut off from the surrounding environment without increasing test-related stress and anxiety. This type of induced arousal suggests the possibility of performing the dynamic evaluation with a reduced dose of the drug or with simple oral agents in place of intracavernosal injection (Pescatori[8] et al. 2000; Park[9] et al. 2002). The clinical results are suggestive, but the method is not in very widespread use and needs more extensive confirmation.

Transducers:

High frequency small parts transducers are mandatory, preferably with high density crystals so that an elevated spatial resolution is possible both at grey-scale and color-Doppler ultrasound. Gain and power settings should be optimized so that all structures of the penis are appreciable. Harmonic imaging and 3D reconstruction techniques can be

used, if available, but they are not mandatory for the diagnosis even though they can offer a more detailed image of the small post-cavernosal arteries, which are frequently compromised in subjects with diabetes or systemic arterial disease.

Vasoactive Drug Delivery:

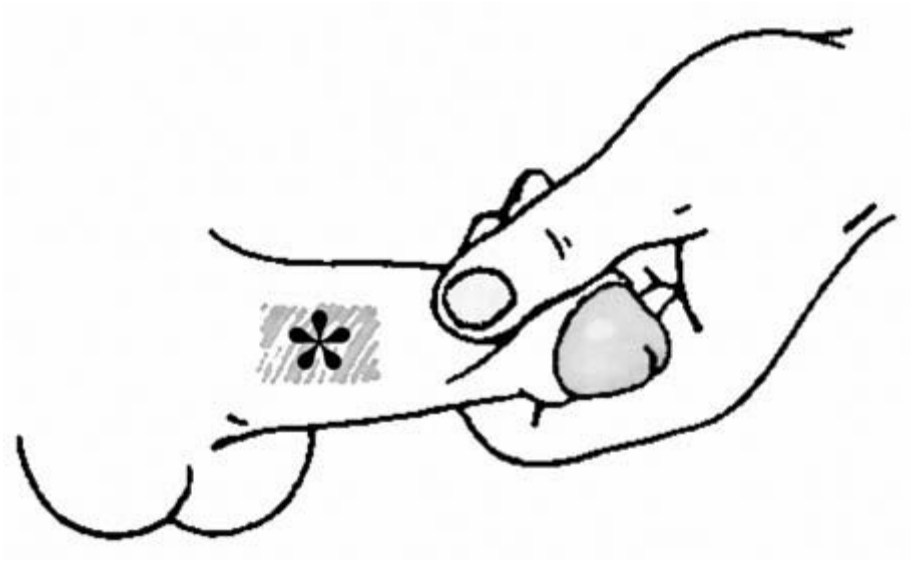
A variety of techniques have been suggested for delivery of vasoactive drugs in patients with erectile dysfunction undergoing color Doppler evaluation. While the most commonly used method is intracavernosal injection, other modalities such as transurethral and transdermal drug delivery have been considered, in the attempt to reduce the invasive character of the study, and risk of possible complications.

Intracavernosal Injection:

Intracavernosal injection of vasoactive substances (dynamic penile ultrasonography) is one of the most important phases in the examination of patients with erectile dysfunction. This minimally invasive procedure is associated with anxiety and apprehension that may negatively influence the erectile response and cause false-positive results. The substances used in the clinical practice vary in composition, dose and mechanism of action (Meuleman[10] et al. 1992). Sometimes they can be used simultaneously in the same mixture. Currently, the most diffuse product is prostaglandin E1 (PGE1), which is used at doses varying from 5 mcg to 20 mcg. It is a product with a high level of security and safety, because it seldom induces a persistent priapism that requires medical or surgical interventions. The employed dose is selected on the basis of the preliminary clinical assessment, which allows the patients to be divided into two

main groups. The first includes subjects who still have nocturnal erections and some preserved sexual activity; in this group a single dose of 5 or 10 mcg can be sufficient, but, if an incomplete erection is obtained, a second injection can be performed after 30 min to differentiate a real organic erectile dysfunction from an insufficient response to a low dose of the drug (Lehmann[11] et al. 1999; Chen et al. 2000). The second group includes those who report short erections, generally insufficient to perform a complete intercourse. In this case a 20-mcg dose of PGE1 is preferred (Lehmann[11] et al. 1999). Prostaglandins can be responsible for a longstanding erection that lasts 3–4 h associated with pain, which generally disappears spontaneously probably as a consequence of the complete metabolic consumption by the intracavernosal enzymes. Papaverine is the second most used drug to stimulate erections at a dose ranging from 10 to 40 mg. A great individual variability in the response to the same dose has been observed and the time of erection is usually longer than that obtained with PGE1 (Fitzgerald[12] et al. 1991). The most common systemic signs are secondary to peripheral vasodilatation with a sense of heat and occasionally hypotension. These effects are sometimes not tolerated by the patients performing self-injection at home. Focal fibrosis of the erectile tissue or diffuse corporeal fibrosis have been frequently observed and are the consequence of focal or diffuse ischemia of the erectile tissue. For these reasons papaverine is currently not used systematically even though its erectile effect is more intense and the rigidity more evident than with other vasoactive products. The relaxation of the erectile tissue and the vasodilatation obtained with papaverine are generally more evident, probably

because of the higher quantity of nitric oxide (NO) involved. The action of the NO is essentially an arterial vasodilatation, while the effect on the cavernosal musculature is less evident. Other drugs used are phentolamine and phenoxybenzamine, alpha-lytic drugs that produce relaxation of the smooth muscle of the arterial wall and of the erectile tissue. Some authors have proposed the use of a mixture of all three vasoactive substances, whose action is similar, but probably follow different biochemical pathways: papaverine, phentolamine and prostaglandin. The erectile response observed in patients without arteriogenic erectile dysfunction is usually intense and the incidence of priapism frequent. The association called “Trimix” shows a high incidence of complications, and the individual dose is difficult to define. The intracavernosal injection is performed on the lateral aspect of the penis at the proximal or medial third of the shaft. Commonly, a 30-G needle is used and the puncture is performed away from the dorsal nerves of the penis. Intraspongiosal or intraurethral injection should be carefully avoided. Incorrect puncture can produce pain, particularly if performed near the dorsal nerves, or urethral pain/heat, if the product has been injected into the corpus spongiosum. Subcutaneous injections cause less pain and local swelling, but no erection. These complications are more frequently observed in patients at the beginning of self-injection.



Schematic drawing showing the elective site on the lateral surface of the penis (*) where to perform intracavernosal drug injection

Scanning:

Ultrasound examination of the penis in patients with erectile dysfunction is performed with scans at rest, before induced erection and in the erection/tumescence phases. After intracorporal drug injection scans are usually performed after 5, 10, 15 and 20 min at the level of both cavernosal arteries. Scanning is preferably made on the ventral surface, especially when the erection is obtained, because the probe orientation is particularly favorable to study the cavernosal flow. The basal study generally has a low diagnostic yield and can be omitted if a preliminary clinical evaluation has been performed. After drug injection grey-scale scanning is performed that allows a good detection of the cavernosal arteries and evaluation of the cavernosal tissue distension. The septum and the tunica albuginea are well depicted. Afterwards color imaging is performed using a

reduced field of view to maintain a high frame rate. Pulse repetition frequency (PRF) values of 1,000– 1,500 Hz are employed with a low wall filter. Longitudinal scans on the cavernosal arteries are performed with steering of the color box so that a good definition of the blood flow is acquired. The cavernosal arteries have a parallel course to the linear probe with a non-favorable Doppler angle, because of being perpendicular to the direction of flow. The sample volume size is about 1 mm, which is the corresponding measure of the diameter of the cavernosal vessels. Color imaging allows an easy detection of the arteries from the base of the penis down to the retrobalanic zone. Anatomical variations of the cavernosal arteries are present in 20–30% of the patients with double or triple arterial vessels. They can have the same outer diameter or can be different in size and length. The blood velocities measured are dependent of their diameter (Mancini[13] et al. 1996). The helicine arterioles and their branches can be easily detected because of their perpendicular course in respect to the probe. The 3D reconstruction of the intracorporeal vessels allows defining the spatial distribution of the small vessels and a semi quantitative evaluation of the vascular density and of the size of the helicine arterioles, which are frequently compromised in patients with diabetes or systemic vascular pathology. Following identification at color Doppler ultrasound, the cavernosal vessels are interrogated. Pulse-wave (PW) duplex Doppler is turned on putting the sample volume on the cavernosal arteries. The spectral analysis is preferably performed at the base of the penis where the Doppler angle is particularly favorable (between 30° and 50°) and the flow velocity shows major reproducibility and

correctness (Mills[14] and Sethia 1996). The flow velocity must be measured repeatedly (at least three times) at the same level and the mean value reported. Functional studies have shown a progressive decrease of blood velocity in the cavernosal arteries from the base to the glans penis.

Timing:

The time necessary to obtain an erection after pharmacostimulation varies greatly from one patient to another. For this reason continuous monitoring is necessary up to 30–40 min. In some subjects a rapid erection is observed after 5 min, but in the majority of the examinations it is necessary to wait 15–20 min to have a stable erection. If the erection does not realize after 20 min, it is good practice to prolong the test to 30–40 min to exclude late responses. To reduce the time to erection the patient can be invited to stand up and to walk in the ultrasound laboratory. Sexual visual stimulation can be employed with good results (Erbagci[15] et al. 2002). All these maneuvers increase the erection firmness especially in patients with venous leakage because of the increase of the venous pressure in the superficial and deep venous network of the penis (Pescatori et al. 2000; Park et al. 2002).

The introduction of phosphodiesterase-5 (PDE5) inhibitors has revolutionized the therapy of erectile dysfunction and radically changed the way in which patients are investigated (Speel[2] et al. 2001). Documentation of a good quality erection in response to a PDE5-inhibiting drug confirms grossly adequate arterial inflow and effective veno

occlusive mechanisms. However, Doppler interrogation of penile vessels continues to have a role in the evaluation of specific patients presenting with erectile dysfunction, in particular, in trauma patients and in patients with Peyronie's disease.

Sonographic anatomy and hemodynamics of penile vasculature

Grey-Scale Ultrasound Anatomy:

The different anatomical features of the penis are better evaluated during tumescence and erection (Lue[62] et al. 1985). In the flaccid state, the corporal bodies present at ultrasonography as cylindrical structures with intermediate echogenicity and homogeneous echotexture. The corpus spongiosum and the glans are more echogenic than the corpora cavernosa. When collapsed, the urethra appears as a transverse line. The echogenicity of the corpora cavernosa progressively decreases during tumescence starting from the region surrounding the cavernosal arteries because of sinusoids dilatation. During maximal penile rigidity, a fine echogenic network is appreciable in the corpora cavernosa due to sinusoidal interfaces. Sinusoidal spaces at the base of the penis are normally larger that in the remaining portions of the shaft. Blood entrapped within the sinusoids often appears slightly corpusculated. The Colles' fascia is barely visible in normal patients. The tunica albuginea and the Buck's fascia are stuck together and appear as a thin echogenic line surrounding the corpora, which became thinner during erection. Two distinct layers become appreciable only when fluid extravasation accumulates between them or very high frequency transducers are used. Vascular structures, however, may provide a suitable interface to separate small portions of the

Buck's fascia from the underlying tunica albuginea in normal penises as well. In particular, the Buck's fascia becomes visible at ultrasound near dilated circumflex veins, and a subtle echogenic line representing the Buck's fascia is usually recognized in the dorsal aspect of the penis dividing the plane of the deep vessels from that of the superficial vessels (Lue[62] and Tanagho 1987; Mueller and Lue 1988) and near the corpus spongiosum. The penile septum appears as an echogenic structure with back attenuation dividing the corpora cavernosa that can hamper visualization of the tunica albuginea in the dorsal aspect of the penis. The intracavernous pillars are recognizable on transverse scans as straight echogenic lines thicker than the sinusoidal walls, which run from one side to the other of the tunica albuginea. The distal penile ligament, an aggregation of the outer longitudinal layer of the tunica albuginea that acts as a buttress for the glans penis (Hsu[42] et al. 2004; Hsu et al. 2005), is recognized at ultrasound as a linear structure more echogenic than the surrounding glanular tissue located centrally within the glans dorsal to the distal urethra. Several penile vessels can be identified at grey scale ultrasound as well. In particular, the cavernosal arteries appear as a pair of dots located slightly medially in each corpus cavernosum. On longitudinal scans they present as narrow tubular structures with echogenic wall (Quam[41] et al. 1989). The diameter of the normal cavernosal arteries ranges from 0.3 to 05 mm in the flaccid state and increases to 0.6–1.0 mm after an intracavernosal injection of vasoactive agents. During the onset of erection, cavernosal artery pulsation is evident in normal subjects (Lee[42] et al. 1993; Kim 2002). The dorsal arteries are visible in the dorsal aspect of the

shaft as anechoic structures with a similar diameter to the cavernosal arteries. As occurs for the cavernosal arteries, also the diameter of the dorsal arteries increases during erection, but to a lesser extent compared with the cavernosal arteries (Lee et al. 1993). Dorsal veins present with less echogenic wall compared to the arteries.

Duplex Doppler Interrogation:

Different Doppler waveforms are recognized in the cavernosal arteries while flaccid and during erection (Fitzgerald[12] et al. 1991; Schwartz et al. 1991; Kim 2002). Peak systolic velocity varies significantly according to the sampling location. In general, velocity values are highest at proximal sites and decrease progressively at distal sites of measurement (Chiou[50] et al. 1999). As a consequence, standardization of the sampling location is needed to reduce the variability of duplex Doppler interrogation of the cavernosal arteries, which is performed at the origin, where they angle posteriorly toward the crus, and a favourable Doppler angle is obtained (Kim[57] 2002).

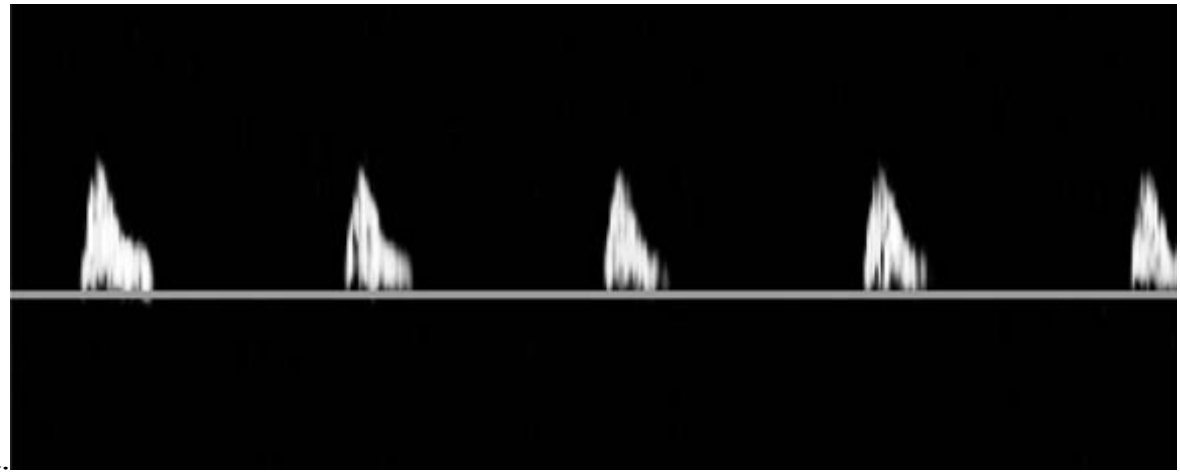
Cavernosal Arteries:

These vessels present during the onset of erection with characteristic progression of Doppler waveform reflecting blood pressure changes within the cavernosal bodies. Spectral waveform changes have been classified into six phases scored from 0 to 5 (Schwartz et al. 1991). In the flaccid state (phase 0) monophasic waveforms are recognized in the cavernosal arteries with low velocity, high resistance flow, typically of 15–25 cm/s. With the onset of erection (phase 1), there is an increase in systolic and diastolic flows. Peak systolic velocity >35 cm/s and diastolic velocity >8 cm/s are

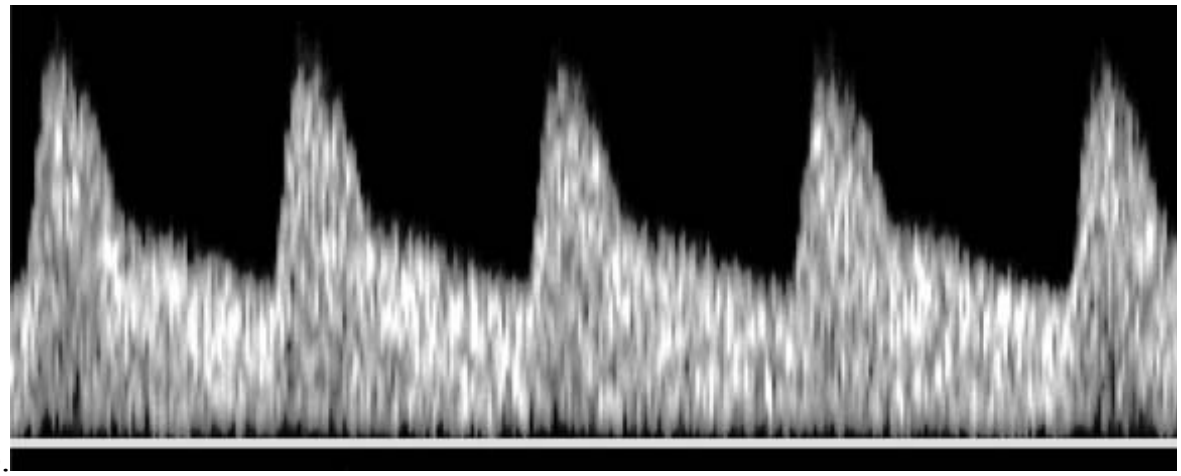
usually recorded in normal subjects in this phase. Peak systolic velocities as high as 80–100 cm/s and diastolic velocities of 20 cm/s or more are often recorded in young patients with normal erections. When the blood pressure within the corpora cavernosa begins to rise, a dicrotic notch appears at end systole, and a progressive decrease of the diastolic flow is observed (phase 2). When the cavernosal pressure equals the diastolic pressure, diastolic flow declines to zero. Holodiastolic flow reversal (phase 4) reflects cavernosal pressure above the diastolic pressure and full erection. During rigid erection the systolic envelope is narrowed and diastolic flow disappears (phase 5). The systolic peak reduces or even disappears, reflecting cavernosal pressure approaching or exceeding blood systolic pressure. Cavernosal phase 5 requires contraction of the bulbocavernous muscles and is not commonly observed after pharmacologically induced erection. The bulbocavernous reflex, however, can be stimulated with compression of the glans penis (Broderick and Arger 1993). During detumescence diastolic flow appears again.

Normal waveform changes in the cavernosal arteries during the onset of erection.

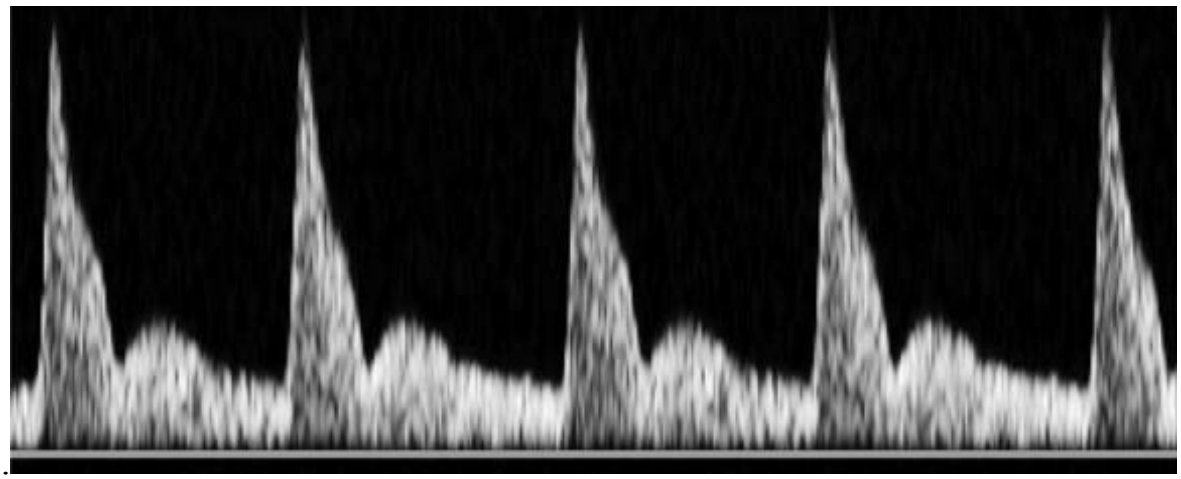
a Phase 0. Monophasic flow with minimal or no diastolic flow occurring in the flaccid state

a. 

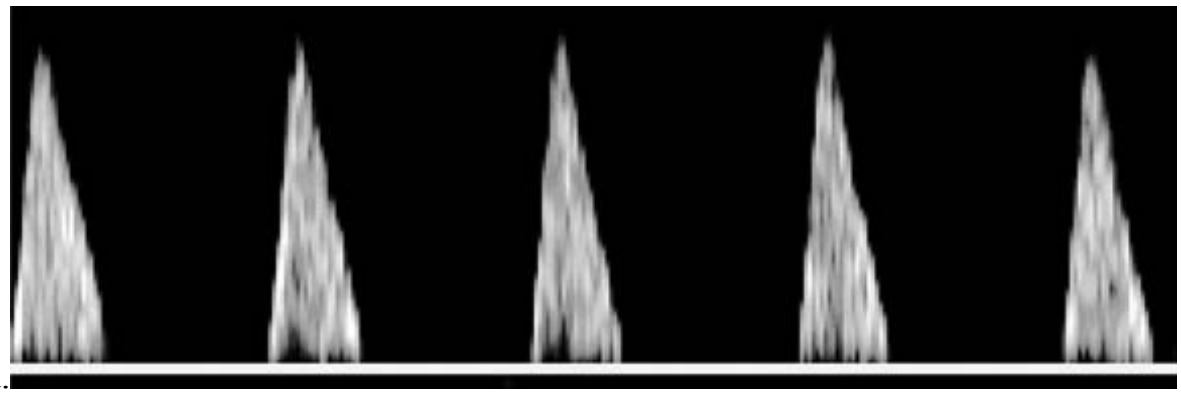
b Phase1. Increased systolic and diastolic flow.

b. 

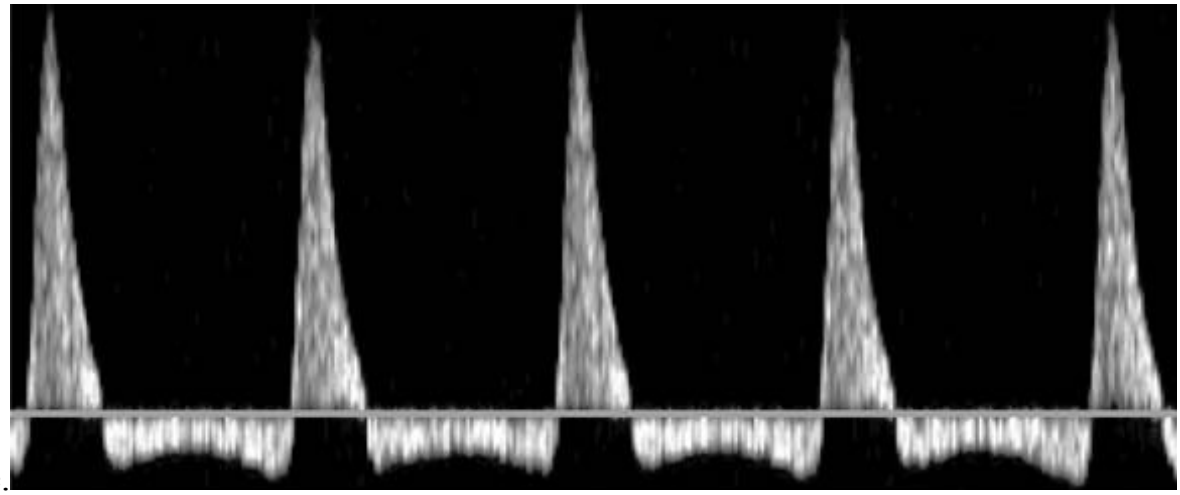
c Phase 2. Dicrotic notch appearance at end systole and progressive decrease of the diastolic flow.

c. 

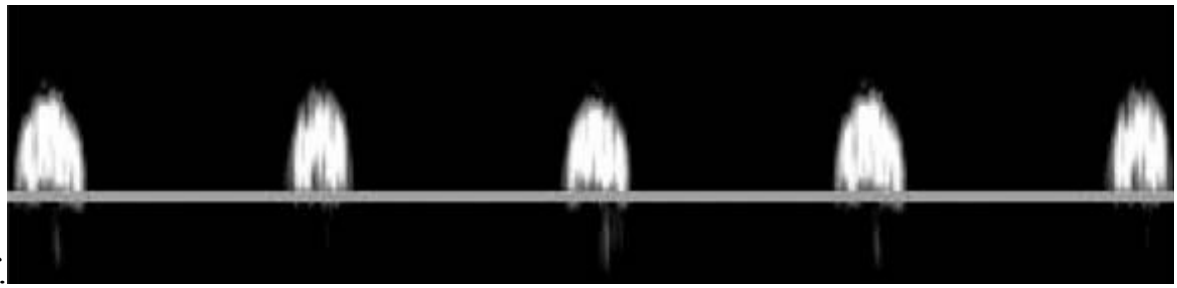
d Phase 3. End diastolic flow disappearance

d. 

e Phase 4. Diastolic flow reversal.

e. 

f Phase 5. Reduction of the systolic peak during rigid erection

f. 

Dorsal Arteries:

These vessels are outside the tunica albuginea and therefore are not subjected to the intracorporeal pressure changes with each phase of erection; therefore, even in well-sustained rigidity, anterograde diastolic flow persists (Broderick and Arger 1993). Generally speaking, Doppler spectral pattern and peak systolic velocity of dorsal penile arteries increase from about 20 cm/s while flaccid to 40 cm/s or more during erection (Lee et al. 1993).

Arterial Communications:

Doppler waveform changes of anastomotic arterial branches, dorsal-cavernous and cavernous-cavernous arterial communications are quite variable, depending on size and position along the shaft.

Cavernosal-Spongiosal Communications:

Also in these vessels characteristic changes are recognized reflecting waveform changes within the cavernosal arteries (Bertolotto et al. 2002). In particular, within the corpus cavernosum cavernosal spongiosal communications have arterial waveforms, and peak systolic velocity increases from approximately 6 cm/s while flaccid to approximately 10 cm/s during erection. The resistive index progressively increases from cavernosal phase 1 to phase 3. When full erection is reached cavernosal-spongiosal communications tend to close and disappear or, in other cases, their diastolic velocity markedly reduces or declines to 0. A characteristic Doppler spectrum can be appreciable with a positive diastolic flow, which can be due to a steel phenomenon towards the corpus spongiosum and an inverse systolic peak that is likely due to the hydraulic “ram stroke” produced near the occlusion site.

Clinical and Doppler evaluation of erectile dysfunction

Classification and Epidemiology:

Erectile dysfunction may be classified as psychogenic, organic (neurogenic, hormonal, arterial, cavernosal and drug-induced), and mixed. Mixed erectile dysfunction is most commonly encountered having both a psychogenic and organic component. Several pathophysiologic states, such as diabetes mellitus, may have detrimental effects upon erectile capacity via multiple pathways. Many epidemiologic studies have described the relationship between erectile dysfunction and increasing age, with a reported prevalence of 40% at age 40, compared to 70% by 70 years of age; for severe erectile dysfunction, rates triple from 5% to 15% for men aged 40 compared to 70 (Feldman et al. 1994[4]). Longitudinal studies within a large cohort demonstrate a non-linear decline for most aspects of sexual function as age increases, with a more pronounced decline in older groups (Araujo et al. 2004[16]). As the latent period between sexual stimulation and erection increases, erections are less turgid, ejaculation is less forceful, ejaculatory volume decreases, and the refractory period between erections lengthens. There is also a decrease in penile sensitivity to tactile stimulation, a decrease in serum testosterone concentration, and an increase in cavernous muscle tone (Kaiser et al. 1988[17]; Rowland et al. 1989; Christ et al. 1990[18]). While relational, psychological, and organic issues are important contributors to erectile dysfunction across age groups, organic issues tend to play a more pronounced role as men age (Corona et al. 2004[19]).

Pathophysiology:

Although psychogenic erectile dysfunction was historically considered to be the most common cause, mixed disorders are most common. Psychogenic erectile dysfunction can be caused by performance anxiety, strained interpersonal relationships, lack of sexual arousability, and overt psychiatric disorders such as depression and schizophrenia. Several studies have confirmed the strong relationship between depression and sexual dysfunction (Araujo et al. 1998[20]; Shabsigh et al. 1998[21]). Erectile dysfunction is noted in patients with neurological disorders such as Parkinson's and Alzheimer's diseases, stroke, and cerebral trauma, often secondary to a decrease in libido or inability to initiate the erectile process. Spinal cord injury patients have varying degrees of erectile dysfunction largely dependent on the location and extent of the lesion. Sensory input from the genitalia is essential to achieve and maintain reflexogenic erection, and this input becomes more important as the effect of psychological stimuli abates with age. Other common causes of neurogenic erectile dysfunction are surgeries that affect the cavernous nerves, such as radical prostatectomy. Androgen deficiency results in a decrease in both nocturnal erections and libido. Although testosterone levels do not correspond to severity of erectile dysfunction, in those patients with reduced libido there are lower levels of testosterone as compared to other patients (Corona et al. 2004). However, erection in response to visual sexual stimulation is preserved in men with hypogonadism, suggesting that androgen is not absolutely essential for erections, due to multiple pathways (Bancroft and Wu 1983[22]; Angulo et al. 2005). Due to the

inhibitory action of prolactin on central dopaminergic activity and the resultant decrease in gonadotropin-releasing hormone secretion, hyperprolactinemia of any cause results in both reproductive and sexual dysfunction (via secondary hypogonadotropic hypogonadism). Vascular pathology may involve lesions of the inflow or outflow mechanisms of penile erection. Erectile dysfunction may be a manifestation of generalized atherosclerosis and may even be its initial presentation. Common risk factors associated with generalized penile arterial insufficiency include hypertension, hyperlipidemia, cigarette smoking, diabetes mellitus, and pelvic irradiation (Rosen et al.1991[23]). Less commonly, local stenosis of the common penile artery may occur in men who have sustained blunt pelvic or perineal trauma (Levine et al. 1990[24]). Dysfunction of the venoocclusive mechanism that normally allows maintenance of erection can cause erectile dysfunction (Rajfer et al. 1988[25]) and may be the result of degenerative changes affecting the penis such as general aging, Peyronie's disease, and diabetes mellitus. Peyronie's disease is more common in middle age, but may be present in the aging male although it tends to be underdiagnosed, especially if there has been a long period without rigid erection. Although generally caused by global penile tissue degeneration, venoocclusive dysfunction may also be the result of congenital or trauma induced formation of large venous channels draining the corpora cavernosa. Venous leak can be seen in anxious men with excessive adrenergic tone causing structural alterations of the cavernous smooth muscle and endothelium and insufficient trabecular smooth muscle relaxation (Christ et al.1990[26]).Finally, venous leak can be seen in patients with

acquired shunts that result from the operative correction of priapism. A variety of commonly used medication7 have been reported to cause erectile dysfunction. Central neurotransmitter pathways, including serotonergic, noradrenergic, and dopaminergic pathways involved in sexual function, may be disturbed by antipsychotics, antidepressants, and antihypertensive drugs. Although any antihypertensive agent could theoretically cause erectile dysfunction by decreasing the availability of blood to the corporal arteries (i.e., a pressure-head phenomenon), differences are noted between various classes of medications, with less erectile dysfunction associated with angiotensin- converting enzyme inhibitors and selective beta-adrenergic blocking drugs (Grimm et al. 1997; Papatsoris and Korantzopoulos 2006; Shiri et al. 2006[28]). Non-selective beta-adrenergic blocking drugs may cause erectile dysfunction by potentiating alpha-1 adrenergic activity in the penis as well as by a possible central mechanism (Horowitz and Goble 1979[29]). Thiazide diuretics have been reported to cause erectile dysfunction by an unknown mechanism (Chang et al. 1991[30]). Spironolactone, acting as an anti-androgen, can cause a decrease in libido and gynecomastia as well as causing erectile dysfunction. Cimetidine, a histamine-H2 receptor antagonist, has been reported to decrease libido and cause erectile failure; it acts as an anti-androgen and can cause hyperprolactinemia (Wolfe 1979[31]). Other drugs known to cause erectile dysfunction are estrogens and drugs with anti-androgenic action such as ketoconazole and cyproterone acetate. In many disease states, the associated erectile dysfunction may be due to multiple causes. About 50 percent of men with chronic diabetes mellitus are reported to

have erectile dysfunction. In addition to the disease's effect on small vessels, it may also affect the cavernous nerve terminals and endothelial cells, resulting in a deficiency of erectogenic neurotransmitter release. Additionally, in diabetics, corporal smooth muscle relaxation in response to neuronal- and endothelial-derived nitric oxide (NO) is impaired and may be secondary to the accumulation of glycosylation products (Saenz De Tejada[32] et al. 1989; Seftel et al. 1997; Cartledge et al. 2001; Angulo et al. 2003). The pathophysiology of erectile dysfunction in DM is multifactorial, consisting of vascular, neurological, endothelial, and hormonal insults. The penile microvasculature is very sensitive to insults that affect other sites in the vascular system. DM is associated with atherosclerosis of both large and small penile vessels. Several studies point to corporal and pudendal arterial insufficiency as a common finding on both Doppler ultrasound and angiographic studies (Herman[33] et al. 1978; Wang et al. 1993). DM affects a variety of nerve fibers, and histologic studies in animals and humans have demonstrated quantitative and qualitative changes in penile nerves (Faerman[34] et al. 1974; Italiano et al. 1993; Morano 2003). On a cellular level, neurotransmitter abnormalities have been found in both human diabetics as well as in experimental animal models (Ehmke[35] et al. 1995; Vernet et al. 1995). In diabetics, corporal smooth muscle relaxation in response to neuronal- and endothelial-derived nitric oxide (NO) is impaired and may be due to the accumulation of glycosylation products (Saenz De Tejada et al. 1989; Seftel et al. 1997; Cartledge[36] et al. 2001; Angulo et al. 2003). Although the data are somewhat conflicting, there may also be decreased production of NO (Ehmke et al. 1995). Additionally, animal

and human studies have demonstrated hypogonadism in diabetics, which may contribute to both erectile dysfunction and decreased libido; however, this tends to be mild and likely does not play as great a role as the neuronal and vascular injuries (Murray[37] et al. 1987; Murray et al. 1992). Reduced libido may also be a significant etiology for ED in DM, although this has not been studied in conjunction with testosterone levels (Nakanishi[38] et al. 2004). Chronic renal failure is also frequently associated with diminished erectile function, impaired libido, and infertility. The mechanism is probably multifactorial: low serum testosterone concentrations, diabetes mellitus, vascular insufficiency, multiple medications, autonomic and somatic neuropathy, and psychological stress. Men with angina, myocardial infarction, or heart failure may have erectile dysfunction from anxiety, depression, or concomitant penile arterial insufficiency. Social drugs including cigarettes and alcohol also affect erectile function. Cigarette smoking may acutely induce vasoconstriction and penile venous leakage because of its contractile effect on the cavernous smooth muscle (Juenemann[39] et al. 1987); more importantly, chronic use may accelerate atherosclerotic changes in the penile microvasculature. Alcohol in small amounts may improve erections and increases libido because of its vasodilatory effect and the suppression of anxiety; however, large amounts can cause central sedation, decreased libido, and transient erectile dysfunction. Chronic alcoholism may cause hypogonadism and polyneuropathy, which may affect penile nerve function (Miller[40] and Gold 1988). As physicians, we may cause erectile dysfunction through the medications we prescribe and the surgeries we perform. Pelvic

surgeries, particularly radical prostatectomies, frequently cause erectile dysfunction; analogous to diabetes mellitus, as described above, the erectile dysfunction may be the result of multiple pathophysiologies despite one underlying insult. Despite surgical advances in preservation of the cavernous nerves (Walsh[41] and Donker 1982), only 20% of patients return to pre-procedural erectile function a year after prostatectomy (Hu[42] et al. 2004). Even in nerve-sparing procedures, postoperative neuropraxia results in a cascade of events including loss of nocturnal erections, smooth muscle apoptosis, increased fibrosis, and eventual anatomic changes leading to venous leakage (Mulhall et al. 2002; Leungwattanakij et al. 2003; Iacono et al. 2005). Erectile dysfunction may be the first manifestation of many diseases including diabetes mellitus, coronary artery disease, hyperlipidemia, hypertension, spinal-cord compression, pituitary tumors, and pelvic malignancies. For example, a recent prevalence study found that men with erectile dysfunction were twice as likely to have DM and concluded that erectile dysfunction may be used as an early marker for DM. This relationship was particularly strong in the younger age groups, in which the odds ratio of having DM was 3 (Sun[31] et al. 2006). Two earlier studies found that 11% (Maatman[32] et al. 1987) and 12% (Deutsch[33] and Sherman 1980) of impotent men were found to have previously undiagnosed DM.

Definition:

Erectile dysfunction has been defined by the National Institute of Health (NIH) as the inability to achieve and/or maintain an erection for satisfactory sexual intercourse.

Discordant data have been reported on erectile dysfunction epidemiology with prevalence ranging from 12% to 52%. A recent study reported a prevalence of 12.8% in Italy (Foresta[34] et al. 2005). French epidemiological studies estimate that the prevalence of erectile dysfunction is between 11% and 44%. Prevalence surveys show a correlation with age: the relative risk of erectile dysfunction increases by a factor of 2 to 4 between the ages of 40 and 70 years (Costa[35] et al. 2005).

Clinical Features:

Erectile dysfunction is a multi-factorial disorder and a common presentation for several systemic illnesses, particularly vascular occlusive diseases such as diabetes, arterial hypertension, and atherosclerosis. Few patients consult their doctor, and only a small proportion of them receive treatment. Only few doctors take the initiative to discuss the question of their patients' sex life (Costa et al. 2005). In fact, the clinician must be familiar with the pathophysiologic mechanisms of erectile dysfunction, its associations with other systemic diseases, the indications for specialist referral, and the role of specialized testing to diagnose and treat this disorder effectively (Lobo[36] and Nehra 2005). The andrologist's cultural baggage must include the ability to identify the pathology that can determine erectile dysfunction and the capacity to program a specific diagnostic workup (Foresta et al. 2005). Demonstration of erectile disorders represents an excellent opportunity to conduct a general workup. In fact, management of erectile dysfunction is integral parts of preventive medicine since more than one-third of patients ignore their underlying health problem (Costa et al. 2005).

Diagnosis of Erectile Dysfunction:

Baseline diagnostic evaluation for erectile dysfunction can identify the underlying pathological conditions and associated risk factors in 80% of patients. Such screening may diagnose reversible causes of erectile dysfunction and also unmasks medical conditions that manifest with erectile dysfunction as the first symptom (Hatzichristou[37] et al. 2002). The clinical evaluation of patients with erectile dysfunction should be thorough and systematic, with attention to the appropriate use of sexual symptom questionnaires and symptom scales, detailed medical and sexual history, physical examination, and basic screening laboratory tests. Still open is the question of which specific tests such as tumescence and rigidity measurements, intracavernous administration of vasoactive drugs and color/duplex Doppler sonography are required for adequate clinical assessment.

Preliminary Clinical Assessment:

Prior to instrumental or invasive procedures, patient reported assessment should be performed. Patient self report, administered questionnaires, event logs or simple patient diaries are commonly used for the diagnosis of erectile dysfunction (Rosen et al. 2006). The International Index of Erectile Function (IIEF) questionnaire can be used to measure the erectile function (Rosen et al. 1997). It simplifies the preliminary assessment and can help to evaluate and define the cause of the erectile dysfunction and identify the underlying vascular issue. Even though the IIEF questionnaire was originally proposed to evaluate the results of treatments, it can also be used in clinical practice to evaluate

the erectile function in all patients attending ultrasound investigation. The questionnaire has been shown to be highly versatile and can be employed in all patients with erectile dysfunction regardless of the cause, co-morbidities and cultural background.

A simplified and reduced version has been developed called the Sexual Health Inventory for Men (SHIM), and is used in clinical practice as a valid method to evaluate the severity of erectile dysfunction (Rosen et al. 2002). The SHIM score also allows the efficacy of treatment to be monitored. These two indices give a global evaluation of erectile function, but do not assess other sexual disorders since they do not provide information regarding the causes of erectile dysfunction, which can be organic or psychological or secondary to other health issues (diabetes, cardiovascular disease, drugs, neurological disease, etc.). Another important issue in the initial medical and sexual history of the patient regards the erection hardness, which is fundamentally key to erectile function. An Evaluation Hardness Grading Scale (EHGS) can be used, consisting of a self reported measure that classifies erection hardness on a four-point scale (Mulhall et al. 2006). This evaluation is very simple and quick to perform and gives important clinical information of patient satisfaction of his erectile function.

Sexual Health Inventory for Men (SHIM)

SCORES	**1**	**2**	**3**	**4**	**5**
How do you rate your confidence that you could get & keep an erection?	very low	low	moderate	high	very high

How often were your erections hard enough for penetration?	never or almost never	a few times	sometimes	most times	almost always or always
How often were you able to maintain your erection after you had penetrated (entered) your partner?	never or almost never	a few times	sometimes	most times	almost always or always
How difficult was it to maintain your erection to completion of intercourse?	extremely difficult	very difficult	difficult	slightly difficult	not difficult
How often was it satisfactory for you?	never or almost never	a few times	sometimes	most times	almost always or always

Erection Hardness Grading Scale (EHGS)

Grade 1: Increase in size of penis, but not hardness (rigidity)

Grade 2: Increase in size and slight increase in hardness (rigidity), but insufficient for sexual intercourse

Grade 3: Increase in hardness (rigidity), sufficient for sexual intercourse, but not fully hard (rigid)

Grade 4: Fully hard rigid erection

Ultrasound Imaging Findings in Erectile Dysfunction

Several changes are detected in patients with erectile dysfunction that are useful to differentiate among different underlying causes for this condition. In particular, anatomical and vascular alterations can be evaluated at grey-scale and color Doppler ultrasound, as well as pathological spectral changes in the cavernosal arteries and in other penile vessels.

Grey-Scale Ultrasound Findings:

The morphological aspects to define with grey-scale ultrasonography are the presence of calcifications and kinking of the cavernosal arteries; diameter and size changes of the cavernosal arteries before and after pharmacological injection; distension and texture of the erectile tissue evaluated before and during erection. In older patients, and in those suffering from diabetes or chronic renal failure, micro calcifications in the wall of the cavernosal arteries are frequently detectable and are the expression of calcium deposits in atheromatous endothelial plaques or in the tunica media as observed in subjects on chronic hemodialysis. Measurement of the diameter changes in the cavernosal arteries after drug injection is clinically more useful since it expresses the stiffness of the arterial wall. In normal subjects there is normally a 75 to 120% increase in size of the vessels whose diameter is of 0.5–0.7 mm at rest and 1–1.2 mm after stimulation. This measurement is performed using the maximum electronic magnification of the scanner to reduce errors due to incorrect positioning of the electronic calipers (Chiou et al. 1999). The size increase of the arteries in patients with arteriogenic ED is usually less

than 75%. The functional response of the vessels to the drug is nonspecific and not always expression of stenosis or obstruction, but can be secondary to a reduced elasticity or contraction of the muscular wall. A normal vascular response is considered when the increase in size is of 100% or more with respect to the basal values. The measurement of the diameter changes of the corpora cavernosa during the different phases of erection is another parameter that has been used. The distension can be asymmetric because of reduced relaxation of the cavernosal tissue on one site due to structural changes (fibrosis) or secondary to unilateral reduced flow because of unilateral arterial obstruction. The measurement of the area of the corpora cavernosa in the transversal scan is simple using the electronic facilities of the ultrasound equipment. It is possible to calculate immediately the area delimitated with the trackball. Actually these measurements are rarely used in the clinical practice because penile changes in size and rigidity are well evaluated clinically and manually (Nelson and Lue 1989).

Color Doppler Imaging:

Color imaging is fundamental to identify the cavernosal arteries and to detect the presence and direction of flow, especially in patients with reduced distension of the vessel after drug stimulation (Mancini et al. 2000). The vessel kinking, stenosis and obstruction are easily identified. Obstructions appear as non-colored segments of the arteries, while stenoses are associated with areas of increased velocity and post-stenotic turbulence. Color Doppler imaging is useful to detect flow in the cavernoso-dorsal and cavernoso-urethral anastomoses, which are common in patients with arteriogenic erectile

dysfunction. Because of extensive arterial lesions, the flow in the helicine arteries is reduced, and sometimes the distal part of the cavernosal arteries is not visualized because of reduced flow velocity (Sarteschi et al. 1998). Power Doppler imaging and the 3D rendering techniques are proposed to detect the arterial wall lesions and the distribution of the elicine arteries in subjects with diffuse lesions of the small intracorporeal vessels as observed in diabetics (Montorsi et al. 1998; Klingler et al. 1999). In patients with venous occlusive erectile dysfunction the cavernosal flow is elevated and easily detected. The vessels show an increased diameter and can be followed for a long course in the center of the corpus cavernosum. The helicine arterioles are numerous and visible up to the tunica albuginea (Hampson et al. 1992). Venous leakage pathways are patent.

Spectral Doppler Imaging:

Spectral analysis is the most important parameter used to characterize the severity and the nature of the erectile dysfunction (Knispel and Andresen 1992). It is possible to calculate semi quantitatively the penile perfusion and indirectly to calculate the intracorporal pressure, which are the main factors that influence the validity and duration of the erection (Shabsigh et al. 1989). There is a general agreement that the peak systolic velocity (PSV) measured at the level of the peno-scrotal junction is the best parameter for a clinical judgment of the arterial perfusion (Oates et al. 1995). PSV above 35 cm/s is considered the expression of a normally functioning arterial tree, even though arteriography can detect atheromatous parietal lesions that are hemodynamically

non-significant. When the Doppler examination reveals a PSV less than 25 cm/s, the erectile dysfunction is considered of arteriogenic origin with a sensitivity of about 100% and a specificity of 95% as shown by the arteriographic studies that correlated flow data with arteriographic images (Valji and Bookstein 1993). Much more complex is the clinical evaluation of patients who show PSV values between 25 and 35 cm/s. This range of values is commonly observed in older subjects with mild erectile dysfunction. Probably they have a stiffness of the arterial walls with intimal thickening and reduced response to PGE1 stimulation, secondary to an endothelial lesion and reduced NO production. In these patients stenosis or obstruction of the precavernosal arteries can be suspected and the flow study of these larger vessels should be performed. The terminal branches of the internal pudendal artery can be explored with a high linear frequency probe positioned in the perineal area under the scrotum. The flow detected at the level of the cavernosal arteries can be asymmetric, and when the difference of PSV is greater than 10 cm/s a unilateral arterial insufficiency must be suspected with secondary flow impairment. When the arterial obstruction is complete, color Doppler imaging can show flow inversion in the cavernosal artery, easily detected in the longitudinal and transversal scans because of the different color of flow. At spectral analysis the flow is reversed in the proximal portion of the artery and normally directed in the distal part. The curve obtained is of low amplitude with increased time to peak. The blood flows from the contralateral patent cavernous artery or from the dorsal artery through transeptal or dorso-cavernosal anastomoses (Wegner et al. 1995). Cavernosal-spongiosal

communications with reversed flow can refill the cavernosal artery retrogradely as well. Spectral curve in patients with arteriogenic erectile dysfunction is characterized by the absence of typical phase variations that can be observed in normal subjects. The flow is reduced and unchanged during the whole scanning time. Valid erections can sometimes be observed in patients with extensive arteriogenic lesions and PSV below 25 cm/s, but with a preserved and active veno-occlusive mechanism that compensates for the reduced arterial inflow. In these cases the beginning of the erection is delayed, but can sometimes be long standing. Veno-occlusive erectile dysfunction is more common in clinical practice and is usually observed in younger patients without arterial disease. As confirmed by cavernosography and cavernosomanometry (Kropman et al. 1992), the diagnosis is made on the basis of a high and persistent peak systolic velocity, which is superior to the cut-off values of 35 cm/s, and end diastolic velocity with a sensitivity of 90–94%. The disappearance or inversion of the diastolic flow is indicative of a correctly functioning veno-occlusive mechanism, and the erectile dysfunction is probably of different origin (hormonal, psychological) (Wespes et al. 1998). The use of the resistive index (RI) to measure the venous function does not show advantages over the simple end diastolic velocity values. RIs of 0.9–1.0 are indicative of normality, while lower values suggest venous leakage. When the RI is below 0.75 end diastolic velocity is generally higher than 10–12 cm/s in 95% of patients. In these cases the venous leakage is persistent and elevated, and there is no efficacy of oral drugs. The presence of an elevated end diastolic velocity is indicative of low intracavernosal pressure, inadequate

to obtain and maintain rigidity sufficient for normal intercourse (de Meyer and Thibo 1998). Less frequently observed are cases of erectile dysfunction of mixed origin, arteriogenic and venous, showing low systolic velocity and persistent diastolic flow. The response to pharmacological stimulation in the dorsal penile arteries is completely different from in the cavernosal. They do not show the typical phase changes detected in the cavernosal arteries and secondary to the intracorporeal pressure (Hwang et al. 1991). The flow is elevated even in full rigidity. They provide blood to the glans, and the peak systolic velocity increases to produce an engorgement of the glans vasculature with secondary distension and stiffness of this part of the penis. Lesions of these vessels can be the cause of reduced tumescence of the glans and of a “soft-tip” during erection. In the deep dorsal vein the flow is always high during all the phases of erection. Commonly it increases after drug injection. The flow velocity measurement is not clinically useful in patients with erectile dysfunction and particularly in those with venous leakage (Virag and Sussman 1998).

Dorsal-cavernosal anastomosis is commonly detected in patients after pharmacologically induced erection, independently of the nature of the erectile dysfunction. The flow direction is normally from the dorsal artery to the cavernosal and the end diastolic velocity is always high and not influenced by the intracorporeal pressure.

Materials and method:

Seventy seven consecutive patients referred from various departments like urology, diabetology, psychiatry and general medical out patient departments were included in the study. All patients had the complaint at least 6 months of erectile dysfunction.

All patients had a detailed clinical history and basic blood chemistry done. Standard questionnaire (Sexual health inventory for men - SHIM) was used to clinically grade the amount of erectile dysfunction. Those subjects with scores less than 21 were included in the study.

The sequence of the study module is as follows:

- All patients to undergo penile Doppler with Inj.Papaverine of standard dose (1mg)
- After one week interval all patients again to undergo penile Doppler with Tab.Sildenafil
- During penile Doppler examination both hemodynamic changes (by colour Doppler and spectral pattern) and clinical assessment were done simultaneously.
- Clinical grading is done using Erection Hardness Grading Scale (EHGS) introduced by Mulhall et al. 2006

Inclusion criteria:

- Subjects with clinically diagnosed erectile dysfunction
- SHIM score less than 21

Exclusion criteria:

- Patients on nitrates
- Congestive cardiac failure

Doppler criteria for erectile dysfunction:

Normal

- PSV:>30cm/sec
- EDV:nil
- No venous leak

Erectile dysfunction

- PSV:<30 cm/se
- EDV:>5cm/sec
- Venous leak

Observation:

The following are the examples of arterial and venous insufficiency pattern of erectile dysfunction.

Arterial insufficiency:

Venous insufficiency:

Age range:

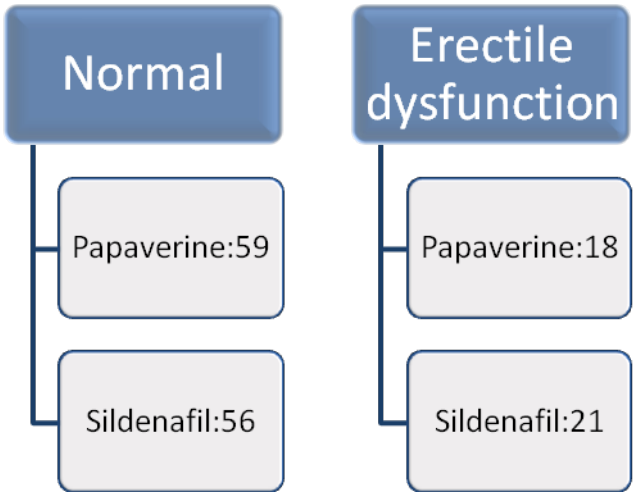
Age range of total number of subjects was from 22 to 65 years with a mean age of 44. According to the SHIM questionnaire the average score of the 77 subjects was 14.6.

Etiology:

Though in vast majority of cases diabetes and hypertension was the causative factor, around 30% of subjects did not have any known risk factors.

Response:

Out of 77 subjects 59 were responding normal to Papaverine(Psv more than 30cm/sec) and 56 to Sildenafil. Papaverine identified 18 subjects as having erectile dysfunction where 21 with Sildenafil.


Normal
Papaverine:59
Sildenafil:56
Erectile dysfunction
Papaverine:18
Sildenafil:21

Response

Clinical grading:

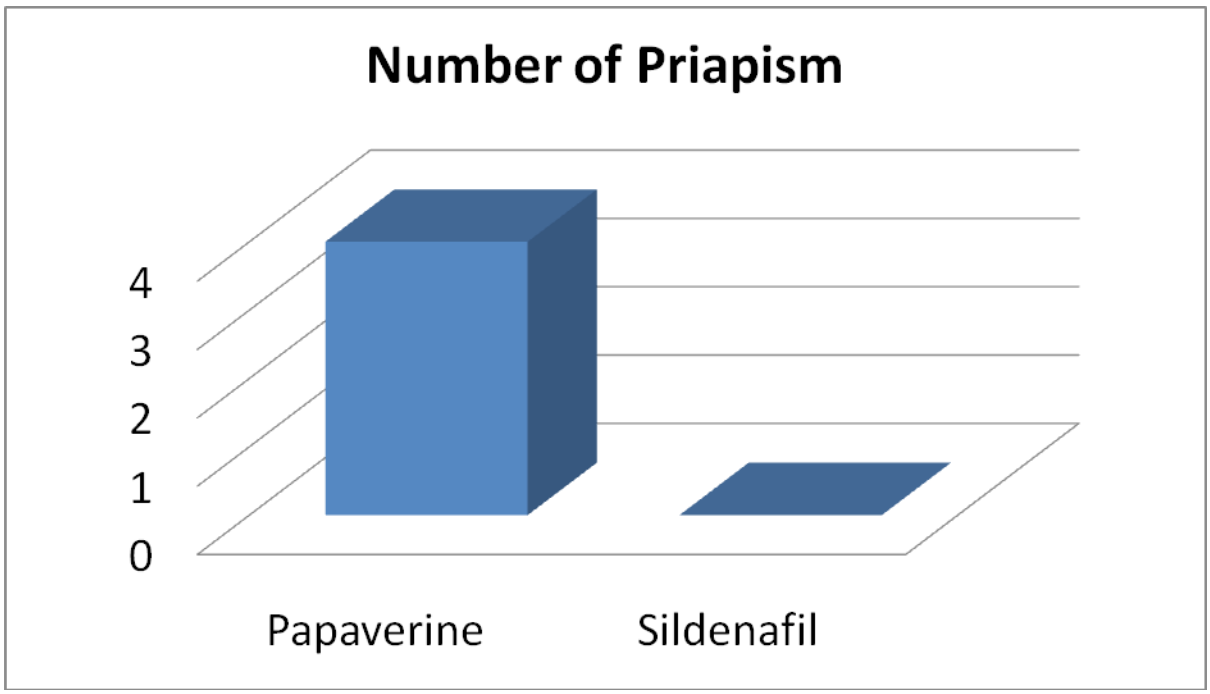
Using Erection Hardness Grading scale(EHGS) the following number of subjects were categorized into 4 grades as follows:

	PAPAVERINE	SILDENAFIL
GRADE 0	18	20
GRADE 1	3	18
GRADE 2	25	31
GRADE 3	31	8

Clinical grading:

Side effects:

Priapism is a known side effect of Papaverine which occurred in 4 subjects in our series. And out of this four 2 needed a surgical management. Sildenafil produced no incidence of priapism. Other side effects were very minor in both of these drugs like mild fleshing and giddiness.



Taking Papaverine as gold standard….

Sildenafil has,

- Sensitivity:91%
- Specificity:85%
- Positive predictive value:95%
- Negative predictive value:75%

Discussion

Normal Doppler study (as defined by attaining a PSV of more than 30 cm per sec and no diastolic flow and no visible venous leak) were obtained in 77% of subjects with Papaverine and 73% of patients with Sildenafil. The difference in the proportion of subjects responding normally among theses two drugs was 3%. This small difference was proven statistically insignificant. So the number of normal responders to both of theses drugs was derived to be equal. Thus Sildenafil gets a sensitivity of 91% taking Papaverine as gold standard.

There were 4 cases of erectile dysfunction due to venous insufficiency when done with Papaverine. But all these 4 cases were identified by Sildenafil as only arterial pattern of insufficiency. Though Sildenafil has got a good sensitivity the fact that it has poor capacity to discriminate between arterial and venous pattern of insufficiency reduces ones diagnostic confidence. The following is one such example:

With Papaverine:

With sildenafil:

Comparison with previous study:

Comparing the previous study by copel et al our study has a larger number of sample volume and thus more reliable in a statistical aspect. Other important difference is that the previous study used audio visual stimulation where as our study had incorporated self tactile stimulation as an adjunct to Sildenafil. Using self tactile stimulation was

comfortable to most of the patients. Percentage of subjects responded normally to Sildenafil was very low compared to that with Papaverine in their study. But in our study the proportions were proven to be statistically equivalent.

Considering clinical grading of erection by erection hardness grading scale (EHGS), very good grades of erection (grade 4) was obtained in 31 subjects with Papaverine and in only 8 patients with Sildenafil. The difference in this proportion is statistically significant enough to say the very good clinical grades of erection was achieved in more subjects when Papaverine is used, comparing to Sildenafil.

Comparison with previous study

	Study by Copel et al	**Our study**
Nature of stimulus used	Audio visual	Self tactile
No of pts attaining normal PSV by sildenafil	46%	73%

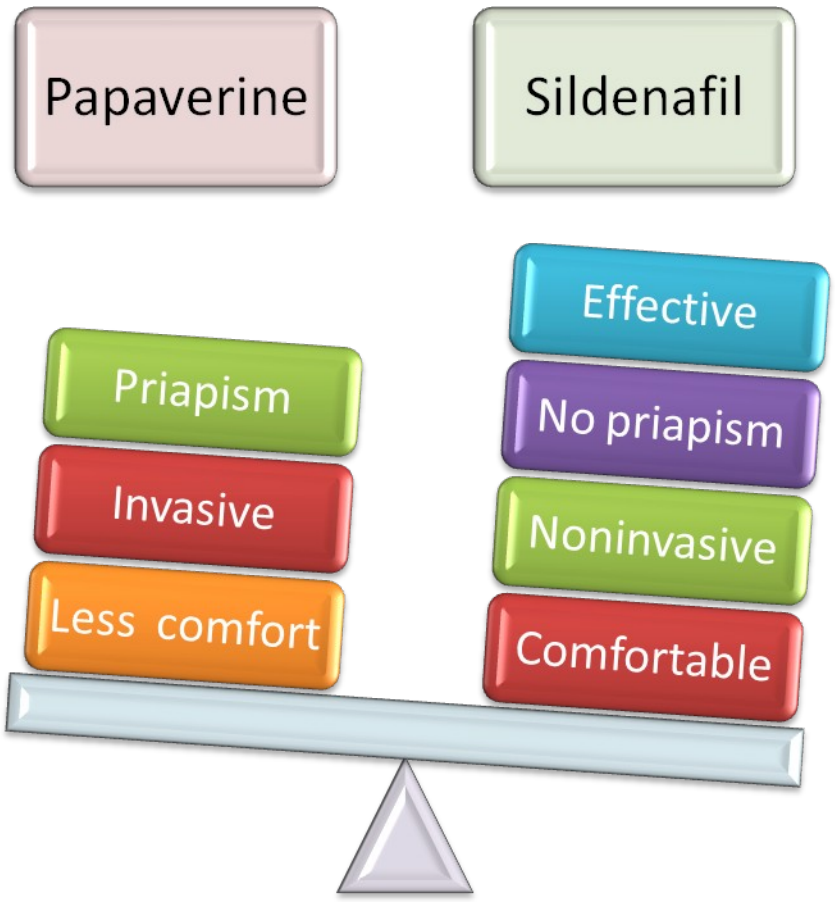
No of pts attaining normal PSV by Papaverine	77%	77%
Statistical difference	Significantly different	Statistically equivalent

There are few limitations in this study. The sample subjects are those with complaints of erectile dysfunction owing to various causes we enumerated previously. Each specific cause is a separate disease entity which is expected to respond in different ways to one or both of these drugs. We could have avoided this only if we had selected a homogenous group of people with erectile dysfunction with a same etiology. There is also no control group. The type of the study is such that we can not have a normal people with out erectile dysfunction to undergo injection of Papaverine and ingestion of Tab.Sildenafil.

Painful priapism is the well known complication of Papaverine. In our series 4 cases of priapism occurred with Papaverine out of which 2 needed surgical management. One went well with vacuum aspiration and other with cavernosa spongeosal shunt. Sildenafil produced no case of priapism among these 77 subjects. Leaving priapism, other complications like sweating, hypotension and nausea were not so frequent with both of these drugs.

Weighing the advantages and disadvantages, sildenafil scores definitely more than Papaverine.

Advantages of Sildenafil



Conclusion

The study becomes unique in that this is the first one of its kind where tab .sildenafil is compared with Inj.Papverine in doing penile Doppler using self tactile stimulation as an adjunct. Another originality of this study is the large number of sample subjects ever used which has helped to avoid statistical bias. The study revealed that there is significant increase in the blood flow of penile vasculature with Tab.Sildenafil, and it could be used as an erectogenic drug in performing penile Doppler when combined with self tactile stimulation. The following facts were derived by analyzing the results:

- Though the proportion of persons getting very good a clinical grade of erection with Sildenafil is significantly low when compared to Inj.Papaverine, the sensitivity is more than 90%.
- Drawback with Sildenafil is that it fails to differentiate when arterial and venous pattern of insufficiency as a cause of erectile dysfunction. All patients with erectile dysfunction due to venous insufficiency with Papaverine were identified as arterial insufficiency with Sildenafil in our study.
- With the given sensitivity, good patient compliance and lower side effects Sildenafil can be preferred over Inj.Papaverine in doing penile Doppler to screen a subject for erectile dysfunction.

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Proforma

Name:

Age:

Duration of symptoms:

Relevant clinical history:

- Possible etiological factors
- Associated co morbidities
- Drugs intake

Basic blood investigations:

- Blood sugar / Urea
- Serum creatinine
- Urinalysis

SHIM score:

B mode USG findings:

Doppler:

Papaverine

Time	PSV	EDV	Venous leak	Interpretation	Clinical grading
1 min					
2min					
3min					
5min					
10min					

Sildenafil:

Time	PSV	EDV	Venous leak	Interpretation	Clinical grading
45 min					
60 min					
90 min					
120 min					
150 min					

Side effects: